

CASE REPORT ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

Pulmonary Langerhans' cell histiocytosis or miliary tuberculosis? Case report and literature review

Early stage pulmonary Langerhans' cell histiocytosis (PLCH) can convincingly mimic miliary tuberculosis (TB), clinically, radiologically, functionally and on histopathological examination, and conversely miliary TB may be mistaken for PLCH. The relevant literature emphasizes mistaking PLCH for TB and vice versa, but does not highlight the possibility of their coexistence. As it is possible for these two entities to present as concomitant disorders in the same patient, a high index of suspicion for TB should be maintained, even when PLCH appears to be the clinically obvious diagnosis, especially when steroid treatment may be used.

Pulmonary Langerhans' cell histiocytosis (PLCH) is a disease of unknown etiology, characterized histopathologically by granulomas containing a large number of Langerhans' cells localized in the lungs.¹ PLCH can mimic tuberculosis (TB) both clinically and on histopathological examination,^{2,3} and conversely TB may be mistaken for PLCH,^{2,4} but the two diseases rarely co-exist in the same patient.⁵⁻¹⁰ The case is reported here of a patient with concurrent PLCH and active miliary TB.

CASE REPORT

A 52 year-old male patient, a smoker (70 pack-years) with an otherwise clear medical history was admitted with a 3-week history of worsening exertional dyspnea, fatigue and dry cough.

The Mantoux test produced a reaction of 14 mm, and auscultation revealed sparse bilateral crackles over the upper pulmonary lobes. The chest X-ray and high resolution computed tomography (HRCT) scan (fig. 1) revealed multiple diffuse nodules 3–6 mm in diameter, mainly in the upper and middle lobes of both lungs. Lung function testing revealed a predominant obstructive syndrome with low DLCO, and mild hypoxemia was present (tab. 1). Bronchoscopy was performed and bronchoalveolar lavage (BAL) revealed an absolute cell count of 20×10^4 /mL with a slight increase of eosinophils (5.2%) and polymorphonuclear cells (3.7%). The count of CD1a positive cells was 5.4% (fig. 2a) with positive S-100 staining, suggestive of PLCH. Ziehl Nielsen staining of sputum specimens and bronchoscopic products (BAL and washing) were negative for acid-fast bacilli (AFB). The serum level of neuron specific enolase (NSE) was increased (21.7 mg/L), but the other tumor markers were within normal ranges. Because of the atypical radiological presentation (lack of cysts),

ARCHIVES OF HELLENIC MEDICINE 2011, 28(6):809–813
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2011, 28(6):809–813

C. Dimitropoulos,¹
I. Vamvakaris,²
D. Vassos,¹
G. Hamalakis,³
C. Gkogkou,²
A. Kokkini,⁴
I. Ntanos¹

¹9th Department of Respiratory
Medicine,

²Department of Pathology,

³Department of 2nd Thoracic Surgery,

⁴Department of Cytology, "Sotiria"
General Hospital of Chest Diseases,
Athens, Greece

Πνευμονική ιστοκυττάρωση
Langerhans ή κεγχροειδής
φυματίωση; Παρουσίαση
περίπτωσης και ανασκόπηση
βιβλιογραφίας

Περίληψη στο τέλος του άρθρου

Key words

Miliary tuberculosis
Pulmonary Langerhans' cell
histiocytosis
Pulmonary tuberculosis

Submitted 14.3.2011

Accepted 27.3.2011

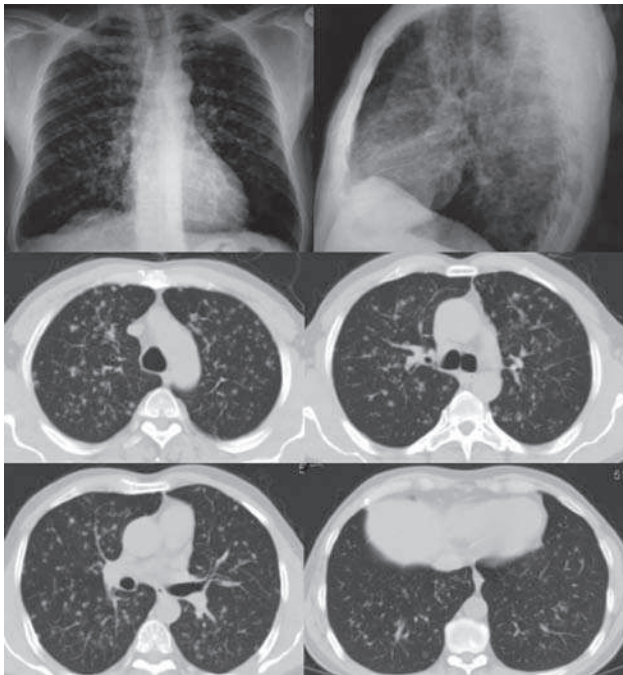


Figure 1. Patient with concurrent pulmonary Langerhans' cell histiocytosis and miliary tuberculosis: Chest X-ray and CT scan: Multiple diffuse nodules 3–6 mm in diameter, with relative sparing of the lower lung lobes.

the marginal CD1a positive percentage and the need for exclusion of other micronodular lung diseases, an open lung biopsy was performed. Histopathological examination revealed PLCH lesions of the cystic type (fig. 2 b–d), with positive CD1a and S-100 staining and negative CMV staining, but no granulomas. The diagnosis of

Table 1. Patient with concurrent pulmonary Langerhans' cell histiocytosis and miliary tuberculosis: Lung function tests and arterial blood gases, before and after treatment.

	Before treatment		After treatment	
	Actual	% (ACT/PRED)	Actual	% (ACT/PRED)
FVC (L)	4.07	91.6	4.96	115.0
FEV ₁ (L)	2.65	74.2	3.33	96.0
FEV ₁ /FVC (%)	65.00		67.00	
FEF _{75–25} (L/s)	1.61	41.5	2.13	2.6
TLC (L)	4.86	69.5	5.46	79.0
RV (L)	2.91	131.0	2.30	103.0
FRC (L)	2.90	83.2	2.66	76.0
DLCO (mmol/min/kPa)	3.46	34.3	8.98	89.0
DLCO/VA (mmol/min/kPa/L)	0.74	51.0	1.24	86.0
pO ₂ (mmHg)	72.00		81.00	
pCO ₂ (mmHg)	36.00		39.00	
pH	7.47		7.41	

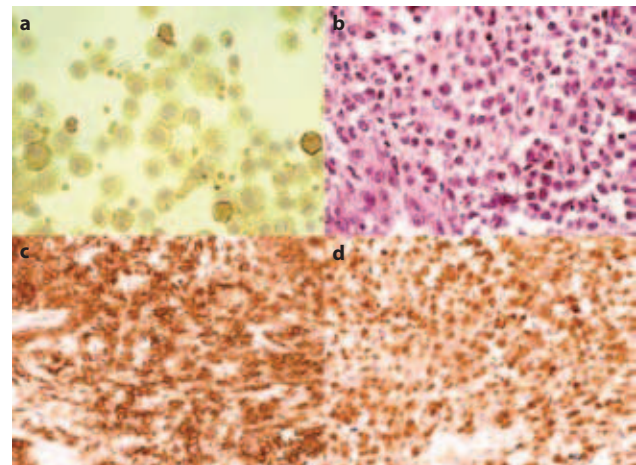


Figure 2. Patient with concurrent pulmonary Langerhans' cell histiocytosis and miliary tuberculosis: (a) BAL immunohistochemistry positive for CD1a (CD1a, x400), (b) Langerhans' cells population with characteristic longitudinal grooves (H-E, x630), (c) immunocytological reaction with the monoclonal antibody CD1a of Langerhans' cells (Peroxidase-antiperoxidase, x400), (d) immunohistochemistry positive for S-100 (S-100, x400).

PLCH and chronic obstructive pulmonary disease (COPD) GOLD stage I was finally established. Immediate smoking cessation was suggested and the patient was discharged to attend follow-up sessions without steroid treatment because of his good general condition. Thyroid gland tests and whole body skeletal scintigraphy with ⁹⁹Tc-MDP were normal. Subsequently, two sputum cultures (Löwenstein Jensen) were positive for *M. tuberculosis* infection. The patient was treated with antitubercular drugs (isoniazid, rifampicin, ethambutol, pyrazinamide), and inhaled bronchodilators-steroids, and stopped smoking. After 6 months of treatment he showed complete resolution of the miliary pattern on chest imaging (fig. 3), improved lung function tests (tab. 1) and no symptoms other than those related to his COPD.

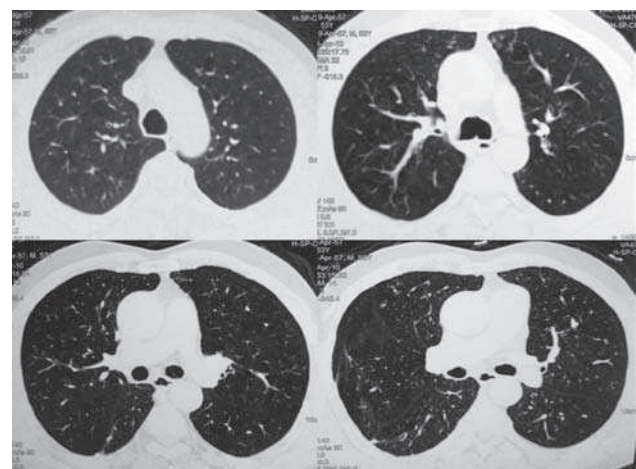


Figure 3. Patient with concurrent pulmonary Langerhans' cell histiocytosis and miliary tuberculosis: Chest X-ray and CT scan: Post-thoracotomy findings, with no miliary pattern.

DISCUSSION

PLCH is a rare disease, representing 3–5% of interstitial lung diseases of unknown etiology.^{11,12} PLCH belongs to a spectrum of diseases characterized by monoclonal proliferation and infiltration of organs by Langerhans' cells.⁴ Isolated type pulmonary disease occurs predominantly in adults and is rare in children. No specific factors such as genes or gender predominance have been related to the disease, except for cigarette smoking, although an infectious etiology has been suggested.⁹

Miliary TB refers to the hematogenous dissemination of tubercle bacilli in primary and post-primary tuberculosis. It is common in immunocompromised patients and is often underdiagnosed in the elderly.⁵

Non-productive cough, exertional dyspnea, weight loss, fever, fatigue and anorexia are the most common symptoms of PLCH, mimicking *M. tuberculosis* infection.^{4,11}

Similarities between these two entities may also appear on radiological examination. Early stage PLCH and miliary TB, in addition to a heterogeneous group of more than 80 conditions, may display a micronodular-miliary pattern on the lung X-ray.¹³ The HRCT findings of PLCH are related to the disease stage.¹¹ The most common early abnormalities are bilateral, symmetrical, peribronchiolar micronodules (1–5 mm) and interstitial infiltration, with predominantly middle and upper lobe involvement.^{4,11} The solid nodules change progressively into cavitated nodules and thick- or thin-walled cysts (less than 20 mm in diameter).^{4,7} Disease progression is accompanied by the development of bullae and subsequent fibrosis yielding a "honeycombing" appearance. In miliary TB, HRCT reveals multiple, well-defined nodules usually appearing in a random pattern, but upper and middle lung predominance has also been reported.¹³ Nodules are usually less than 5 mm, and more often 1–3 mm in diameter. There is no clear correlation between the size and number of nodules on HRCT and the clinical course of the illness, but the presence of adjacent "ground-glass" extension is correlated with dyspnea.¹³ A pre-existing tuberculous lesion or consolidation, with or without cavitation, is sometimes found.

In PLCH, pulmonary function testing data reflect the duration of the disease and the nature of the parenchymal lesions. Patients may present with obstructive, restrictive or mixed dysfunction, but the most characteristic and stable disease finding is that of reduced diffusion capacity, which is observed in 70–100% of patients.¹¹ This reduced diffusion capacity has been associated with the degree of endurance limitation during exercise. The finding of

obstructive dysfunction on pulmonary function testing may also be due to coexistence of COPD, because the majority of patients are smokers. At more advanced stages of the disease, the restrictive pattern predominates, due to extensive fibrosis, although some patients (10–15%) have minimally affected or normal pulmonary function tests despite radiographic lesions.¹¹ In miliary TB major dysfunction on pulmonary testing is represented by restrictive dysfunction and reduced diffusion capacity. These types of dysfunction may remain even after the improvement of radiological findings.

Immunohistochemical reactivity for CD1a or S-100 protein antigens or ultrastructural demonstration of Birbeck granules help in confirming a final diagnosis, but should not be considered as exclusive diagnostic criteria for PLCH, because they have also been reported in other disease processes.⁹ In the appropriate clinical setting, a typical cytomorphological picture can be used alone as definitive evidence of PLCH.^{8,11} A positive value of above 5% CD1a on BAL specimens is suggestive of PLCH, in contrast to lower percentages, which can be found in smokers.¹¹

Serum NSE is known to be elevated in some patients with TB,¹⁴ but there are no data regarding serum NSE levels in PLCH in the literature.

The cornerstone of treatment for PLCH is smoking cessation, which promotes stabilization of the disease and sometimes even improvement of radiological findings.¹¹ In addition, smoking cessation is necessary for the prevention/amelioration of COPD, which often complicates the course of the disease in patients with PLCH. The therapeutic role of corticosteroids has not been yet clearly defined. Studies on small numbers of patients report clinical and radiological improvement from corticosteroid treatment, but without taking into account the benefit of smoking cessation.¹¹ Currently corticosteroid treatment is recommended for progressive disease or in the event of systemic symptoms, but only when smoking cessation has brought no improvement.¹¹ Miliary TB responds to antitubercular treatment, sometimes combined with adjunctive corticosteroid therapy.¹⁵

Incipient PLCH and miliary TB can present clinical, functional, radiological and histopathological similarities. HRCT, in the context of the appropriate clinical setting, is sometimes used for diagnosis of PLCH without histo/cytological confirmation.^{11,12} PLCH can be recognized on HRCT, BAL or histopathological examination, but these procedures alone often cannot exclude the coexistence of other pathological entities, such as TB. The HRCT and BAL findings of the patient presented here were typical of incipient PLCH, although in this case TB was also present.

No granulomas or AFB were found in the histological specimens, which were suggestive only of PLCH. Apart from the miliary pattern, no other parenchymal lesion was revealed on lung imaging suggesting prior or concomitant infection of TB.

Reports in the literature emphasise the difficulties in differential diagnosis between PLCH and TB, but do not mention the possibility of their coexistence. The etiology and pathogenesis of PLCH remains obscure and there are no studies regarding the prevalence of tuberculosis co-infection, although the number of case reports regarding this issue is rising. It is not known whether PLCH predisposes to *M. tuberculosis* infection, or vice versa. Corticosteroid

administration, which is often used in the treatment of PLCH,¹¹ markedly enhances the virulence of *M. tuberculosis* when no specific antituberculous agent is being administered,¹⁷ and this can be perilous in undiagnosed tuberculosis.¹⁸ For this reason a high index of suspicion for unusual entities like TB co-infection should be maintained, even when PLCH seems clinically obvious, especially in countries where the incidence of tuberculosis is high. It is the authors' opinion that the coexistence of TB should be excluded in all patients diagnosed with PLCH, before the onset of steroid treatment. Studies must be also made in order to specify the appropriate timing of steroid treatment when it is indicated, in cases of PLCH with TB co-infection.

ΠΕΡΙΛΗΨΗ

Πνευμονική ιστοκυττάρωση Langerhans ή κεγχροειδής φυματίωση; Παρουσίαση περίπτωσης και ανασκόπηση βιβλιογραφίας

Χ. ΔΗΜΗΤΡΟΠΟΥΛΟΣ,¹ Ι. ΒΑΜΒΑΚΑΡΗΣ,² Δ. ΒΑΣΣΟΣ,¹ Γ. ΧΑΜΑΛΑΚΗΣ,³ Χ. ΓΚΟΓΚΟΥ,²
Α. ΚΟΚΚΙΝΗ,⁴ Ι. ΝΤΑΝΟΣ¹

¹9η Πνευμονολογική Κλινική, ²Παθολογοανατομικό Τμήμα, ³2η Θωρακοχειρουργική Κλινική, ⁴Κυτταρολογικό Τμήμα, Νοσοκομείο Νοσημάτων Θώρακος Αθηνών «Σωτηρία», Αθήνα

Αρχεία Ελληνικής Ιατρικής 2011, 28(6):809–813

Η αρχόμενη πνευμονική ιστοκυττάρωση Langerhans (ΠΙΛ) μπορεί εύκολα να προσομοιάσει με κεγχροειδή φυματίωση (ΤΒ), τόσο κλινικά και ακτινολογικά, όσο και στο λειτουργικό έλεγχο της αναπνοής ή στην παθολογοανατομική εξέταση. Η κεγχροειδής ΤΒ μπορεί επίσης να διαγνωστεί λανθασμένα ως ΠΙΛ. Η υπάρχουσα βιβλιογραφία δίνει έμφαση στη δυσκολία της διαφορικής διάγνωσης μεταξύ των δύο νόσων, αλλά δεν τονίζει την πιθανότητα συνύπαρξής τους. Παρ' όλα αυτά, οι δύο αυτές παθήσεις μπορεί να συνυπάρχουν στον ίδιο ασθενή. Γι' αυτό, ακόμη και όταν η ΠΙΛ είναι κλινικά προφανής, θα πρέπει να διατηρείται επιφύλαξη και καχυποψία για τη συνύπαρξη κεγχροειδούς ΤΒ, ειδικά εάν πρόκειται να χρησιμοποιηθεί κορτικοθεραπεία.

Λέξεις ευρητήριο: Κεγχροειδής φυματίωση, Πνευμονική ιστοκυττάρωση Langerhans, Φυματίωση πνεύμονα

References

- VASSALLO R, RYU JH, COLBY TV, HARTMANT, LIMPER AH. Pulmonary Langerhans'-cell histiocytosis. *N Engl J Med* 2000, 342:1969–1978
- THOMMENSEN P, BARTHOLDY N, BÜNGER E. Histiocytosis X. VIII. Histiocytosis X simulating tuberculosis. *Acta Radiol Oncol* 1983, 22:295–297
- MALASHENKOV EA, MITUSOVA GM, DOROFEEV LA. Case of histiocytosis X mistaken for generalized tuberculosis. *Probl Tuberk* 2001, 4:44–46
- ÖZEN M, AKÇAKAYA N, CAMCIOĞLU Y, ÇOKUGRAS H, OZ B. Isolated pulmonary Langerhans-cell histiocytosis mimicking miliary tuberculosis. *J Pediatr Inf* 2009, 3:135–137
- OKUTAN O, KARTALOĞLU Z, ILVAN A, DENİZ O, SILİT E, GORUR R. Active pulmonary tuberculosis in a patient with Langerhans cell histiocytosis. *Saudi Med J* 2006, 27:401–402
- SPIGELMAN M, PAPI I, DONOGHUE HD. A death from Langerhans cell histiocytosis and tuberculosis in 18th Century Hungary – What palaeopathology can tell us today. *Leukemia* 2006, 20:740–742
- ARAI T, INOUE Y, YAMAMOTO S, AKIRA M, UESUGI H, HAYASHI S ET AL. Incipient stage of pulmonary Langerhans-cell histiocytosis complicated with pulmonary tuberculosis was examined by high-resolution computed tomography. *Respir Med* 2005, 99:1188–1190
- KUMAR S, BATRA C, KATARIA SP, ARORA B, SINGH G, NAYAN RATTAN K ET AL. Langerhans' cell histiocytosis with tuberculosis: A rare combination diagnosed on FNAC. *Ann Diagn Paediatr Pathol* 2007, 11:21–23

9. VIDERAGAY F, MARTINEZ M, MALDONADO P, ZULAICA H, VAZQUEZ E. Langerhans cell histiocytosis and pulmonary tuberculosis, fortuitous association? Case report and review of the literature. *Ann Med Asoc Med Hosp ABD* 2002, 47:38–43
10. DONG SS. Pulmonary Langerhans cell histiocytosis accompanied by active pulmonary tuberculosis. *Korean J Thorac Cardiovasc Surg* 2008, 41:137–140
11. DIAMANTEA F, MERMINGIS D, ROUSSOUT, MERMINGIS C, TSAKANIKAKA K, KARAGIANNIDIS N ET AL. Pulmonary Langerhans cell histiocytosis: Clinical and laboratory findings in 11 Greek patients and review of the literature. *Pneumon* 2007, 20:63–72
12. DAYANANDA L, MOORTHY S, PRABHU NK, SREEKUMAR KP, GHONGADE DV. Pulmonary Langerhan's cell histiocytosis X: A case report. *Ind J Radiol Imag* 2003, 13:275–276
13. ANDREU J, MAULEÓN S, PALLISA E, MAJÓ J, MARTINEZ-RODRIGUEZ M, CÁCERES J. Miliary lung disease revisited. *Curr Probl Diagn Radiol* 2002, 31:189–197
14. SHARMA P, DHINGRA KK, SURAL S, MANDAL AK, SINGH T. Langerhans cell histiocytosis masquerading as tuberculosis: A diagnostic dilemma resulting in inappropriate anti-tubercular therapy. *Pediatr Blood Cancer* 2009, 53:111–113
15. COLLAZOS J, ESTEBAN C, FERNÁNDEZ A, GENOLLÁ J. Measurement of the serum tumor marker neuron-specific enolase in patients with benign pulmonary diseases. *Am J Respir Crit Care Med* 1994, 150:143–145
16. DOOLEY DP, CARPENTER JL, RADEMACHER S. Adjunctive corticosteroid therapy for tuberculosis: A critical reappraisal of the literature. *Clin Infect Dis* 1997, 25:872–887
17. D'ARCY HART P, REES RJ. Enhancing effect of cortisone on tuberculosis in the mouse. *Lancet* 1950, ii:391–395
18. JOHNSON JR, DAVEY WN. Cortisone, corticotropin, and antimicrobial therapy in tuberculosis in animals and man; a review. *Am Rev Tuberc* 1954, 70:623–636

Corresponding author:

C. Dimitropoulos, 9th Department of Respiratory Medicine, "Sotiria" General Hospital of Chest Diseases, 152 Mesogeion Ave., GR-115 27 Athens, Greece
e-mail: xdimitr@yahoo.com

.....